



Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Pharmacoenhancers

Glossary of Terms for Supplement

Carcinogenic = producing or tending to produce cancer

- Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
- Genetic mutations and/or chromosomal damage can contribute to cancer formation.

Clastogenic = causing disruption of or breakages in chromosomes

Genotoxic = damaging to genetic material such as DNA and chromosomes

Mutagenic = inducing or capable of inducing genetic mutation

Teratogenic = interfering with fetal development and resulting in birth defects

Cobicistat (Tybost, COBI)

(Last updated August 6, 2015, last reviewed August 6, 2015)

Cobicistat is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

At cobicistat exposures 7 times and 16 times the human systemic exposure, no increases in tumor incidence were seen in male and female mice. In rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses up to twice the typical human exposure. The follicular cell findings are considered rat-specific, and not relevant to humans.¹

Reproduction/Fertility

No effect has been seen on fertility in male or female rats.¹

Teratogenicity/Developmental Toxicity

Rats and rabbits treated with cobicistat during pregnancy at 1.4 and 3.3 times higher than the recommended human exposure have shown no evidence of teratogenicity.¹

Placental and Breast Milk Passage

No information is available on placental passage of cobicistat. Studies in rats have shown that cobicistat is secreted in breast milk.¹

Human Studies in Pregnancy

Pharmacokinetics

No pharmacokinetic studies of cobicistat have been conducted in pregnant women.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of cobicistat in humans.

Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry, insufficient numbers of first-trimester exposures to cobicistat in humans have been monitored to be able to make a risk determination. Cobicistat is not currently reported separately in the Antiretroviral Pregnancy Registry. All reports of elvitegravir include exposure to cobicistat.²

References

1. Cobicistat (Tybost) [package insert]. Food and Drug Administration. 2014. Available at http://www.gilead.com/~media/Files/pdfs/medicines/hiv/tybost/tybost_pi.pdf. 2014. Accessed July 1, 2015.
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 Jan 1989 - 31 July 2014. Wilmington, NC: Registry Coordinating Center. 2014. Available at <http://www.APRegistry.com>.

Ritonavir (Norvir, RTV)

(Last updated August 6, 2015; last reviewed August 6, 2015)

Ritonavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Ritonavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies in mice and rats have been completed. In male mice, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at levels of 50, 100, or 200 mg/kg/day; based on area under the curve, exposure in male mice at the highest dose was approximately 0.3-fold that in male humans at the recommended therapeutic dose. No carcinogenic effects were observed in female mice with exposures 0.6-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of recommended therapeutic human exposure.

Reproduction/Fertility

No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible because of hepatic toxicity in the rodents.

Teratogenicity/Developmental Toxicity

No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles, was observed in rats; however, these effects occurred only at maternally toxic dosages (exposure equivalent to 30% of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).

Placental and Breast Milk Passage

Transplacental passage of ritonavir has been observed in rats with fetal tissue-to-maternal-serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses.

Human Studies in Pregnancy

Pharmacokinetics

A Phase I/II safety and pharmacokinetic study (PACTG 354) of ritonavir (500 or 600 mg twice daily) in combination with zidovudine and lamivudine in pregnant HIV-infected women showed lower levels of ritonavir during pregnancy than postpartum.¹ Ritonavir concentrations are also reduced during pregnancy versus postpartum when the drug is used at a low dose (100 mg) to boost the concentrations of other protease inhibitors.^{2,3}

Placental and Breast Milk Passage

In a human placental perfusion model, the clearance index of ritonavir was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue.⁴ In a Phase I study of pregnant women and their infants (PACTG 354), transplacental passage of ritonavir was minimal, with an average cord blood-to-maternal-delivery concentration ratio of 5.3%.¹ In a study of cord blood samples from six women treated with ritonavir during pregnancy, the cord blood concentration was less than the assay limit of detection in 5 of the women and was only 0.38 micrograms/mL in the remaining woman.⁵ In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving lopinavir/ritonavir-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks

suggested *in utero* transfer of ritonavir: 2% of infants had detectable plasma ritonavir concentrations at birth while mean infant-to-maternal-hair concentration at 12 weeks postpartum was 0.47 for ritonavir.⁶ However, transfer during breastfeeding was not observed, with no infant having detectable ritonavir plasma levels at 12 weeks.

Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to ritonavir have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with ritonavir. Among cases of first-trimester ritonavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.4% (60 of 2,542 births; 95% CI, 1.8% to 3.0%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁷

References

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4. Casey BM, Bawdon RE. Placental transfer of ritonavir with zidovudine in the ex vivo placental perfusion model. *Am J Obstet Gynecol*. 1998;179(3 Pt 1):758-761. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9757985>.
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7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 Jan 1989–31 July 2014. Wilmington, NC: Registry Coordinating Center. 2014. Available at <http://www.APRegistry.com>.